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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,101	DUBINETT ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed September 15, 2009, is acknowledged and has been entered. Claim 32 has been amended.

2. Claim 32 is pending in the application.

Grounds of Objection and Rejection Withdrawn

3. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed November 21, 2008.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. The rejection of claim 32 under 35 U.S.C. 101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, is maintained.

Beginning at page 13 of the amendment filed September 15, 2009, Applicant has traversed the propriety of maintaining this ground of rejection, arguing in brief that the claimed process has utility since it is used to treat tumor in human patients.

Applicant's arguments have been carefully considered but not found persuasive of the following reasons:

As before noted, the considerations that are made in determining whether a claimed invention is supported by either a specific and substantial asserted utility or a well-established utility are outlined by the published Utility Examination Guidelines

(Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: http://www.gpoaccess.gov/.

Again, a "specific and substantial" asserted utility is an asserted utility that is specific to the particular nature and substance of the claimed subject matter, and which would be immediately available for application in a "real-world" context by virtue of the existing information disclosed in the specification and/or on the basis of knowledge imparted by the prior art, such that its use would not require or constitute carrying out further research to identify or reasonably confirm its usefulness in this context. A "well-established" utility is a credible, specific, and substantial utility, which is well known, immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art.

As presently amended, claim 32 is drawn to a method of attracting T lymphocyte or mature host dendritic cells to a site of *a spontaneous syngeneic tumor* in a mammal, said method comprising obtaining dendritic cells from the mammal, introducing a polynucleotide encoding a secondary lymphoid tissue chemokine comprising the amino acid sequence of SEQ ID NO: 1 into the dendritic cells and placing the cells at the site of the tumor in the mammal.

It is again important to note the distinction between a "syngeneic" tumor and a "autologous" tumor in order to understand that the process that is claimed is but a mere tool for research and otherwise lacks a specific and substantial utility, as is required under 35 U.S.C. § 101 for the patentability of a process.

The term "syngeneic" is a term of art, which, when used in the context of the language of the claim, describes a tumor or a tumor cell line that originated in and was derived from an animal of an identical genetic background as the animal into which the same tumor cells are inoculated so as to establish a tumor in the animal for the purposed of modeling the pathology of the disease associated with the tumor[1].

[1] Though the term "syngeneic" is not expressly defined in this application, it appears that it is used in a manner consistent with its art-recognized meaning.

One description of the derivation of such tumor cells for use in producing animal models for studying adoptive immunotherapy is found in the publication of Shu et al. (*Cancer Res.* 1985 Apr; **45**: 1657-1662). Shu et al. describes the induction of a series of tumors in a particular strain of mice (i.e., "C57BL/6") by injecting the mice with a tumorigenic substance, namely 3-methylcholantrene (MCA); see entire document (e.g., the abstract; and page 1657, column 2). Following their appearance in the mice samples of the tumors were acquired and used to produce two weakly immunogenic, syngeneic tumor models; see, e.g., the abstract; and page 1657, column 2. Shu et al. explain that unlike highly immunogenic, syngeneic and allogeneic[2] tumor models, such weakly immunogenic syngeneic tumor models provide investigators with unique opportunities for studying the adoptive immunotherapy of established tumors; see, e.g., the abstract; and page 1657, column 2.

In part, the reason that poorly immunogenic, syngeneic tumor models are so useful is that such models more accurately mirror the disease that occurs, particularly in human patients. In general, tumor cells tend to dedifferentiate, so as to become less immunogenic over time, which causes the cells to become more indistinguishable from the normal cells of the body and more capable of evading recognition by the immune system.

Allogenic tumor models are established in mice using heterologous tumor cells, which originated in genetically dissimilar, antigenically different individual animals; as a consequence of the tumor cell's intrinsic antigen heterogeneity, the host animal's immune system tends to more readily recognize the tumor cell as foreign to the body[3].

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[2] "Allogenic" is a term of art describing genetically dissimilar, antigenically different individuals of the same species of animal, or the cells and tissues of such different individuals, such as the mice of any of the genetically different strains often used in the art, including, for example, C57BL/6 and BALB/c.

[3] The deficiency of non-syngeneic animal models is explained in the disclosure at paragraph [0004] of the published application, which discloses: "Unfortunately, many animal models of cancer which introduce cancer cell lines into an animal are confounded by immune responses that are influenced by differences between the genetic background of the host animal and the cancer cell lines that are being evaluated. Specifically, in cancer models in which host animals and cancer cell lines do not share an essentially identical genetic background, there are a variety of problems including those associated with "non-self" immune responses by the host's immune system that are akin to those seen in the rejection of transplanted organs between individuals. The non-self immune responses that can result from the host immune system's recognition of non-self antigens on autogeneic cancer cells (a phenomena which

In marked contrast to the evident artificiality of such allogeneic tumor models, tumors occurring in human patients are "autologous"; i.e., the tumors originate from the cells of the selfsame individual. As a consequence, tumors occurring in patients are generally not highly immunogenic, and as noted above, tend to become less immunogenic over time.

Thus, it is oft agreed that syngeneic tumor models or perhaps more preferably weakly immunogenic, syngeneic tumor models are more effectively used to study the pathology of the disease that occurs in humans[4].

Perhaps not inconsistently, at paragraph [0009] of the published application, the specification discloses: "There is a need in the art for cancer models that faithfully mimic immune mechanisms in cancer in order to examine, for example[,] how host cytokine profiles are modulated by SLC as well as the capacity of SLC to orchestrate effective cell-mediated immune responses to syngeneic cancer cells."

As such, this application describes the development and use of *a syngeneic animal model*, which is intended for use in demonstrating that the intratumoral injection of dendritic cells engineered to express high levels of murine secondary lymphoid tissue chemokine (mSLC) promotes chemotaxis of T cells and mature dendritic cells to the site of the tumor in mice[5].

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understandably does not occur in cancers), create an immune response to cancer cells that does not occur in human cancers."

[4] As an example of such indications for syngeneic animal models, Gelderman et al. (*Mol. Immunol.* 2003; **40**: 13-23) teaches immunotherapy offers a potential means for destroying metastatic cancer cells, but despite promising results obtained using xenograft models, the overexpression of mCRP impedes complement-mediated destruction of tumor cells; and because mCRP operates in a species selective manner, "a syngeneic animal model is needed to investigate the contribution of mCRP in monoclonal antibody-mediated immunotherapy" (abstract); see entire document.

[5] Example 10 at paragraphs [0220] and [0221] describes experiments in which the intratumoral injection of transfected, recombinant dendritic cells expressing murine SLC led to eradication of established syngeneic tumors in mice, but there appears to be no directed evidence supporting the conclusion that the eradication of the tumor was achieved by recruitment of T lymphocytes or mature dendritic cells to the sites of the tumors in the mice. Notably though it appears that the specification does not expressly teach that the dendritic cells were transfected with nucleic acid encoding *mouse* SLC, the nature of the nucleic acid used in these experiments is more completely described elsewhere; see, e.g., Sharma et al. (*J. Immunol.* 2000; **164**: 4558-4563) (of record; cited by Applicant), Riedl et al. (*Proc. AACR.* 2003; **44**: 417; abstract #1834), and Reidl et al (*Mol. Cancer.* 2003 Nov 2; **2**:35; as published on the Internet, pp. 1-13).

Accordingly, at paragraph [0010] of the published application, the specification discloses:

> The invention disclosed herein provides **animal models** [emphasis added] which faithfully mimic immune mechanisms in cancer by utilizing host animals and cancer cells that have an essentially identical genetic background. These models are used to demonstrate the capacity of SLC to orchestrate effective cell-mediated immune responses to syngeneic cancer cells. In addition, these models can be used to evaluate host cytokine profiles that are associated with SLC modulated immune responses to syngeneic cancer cells.

The claimed process utilizes such syngeneic tumor models[6], but comprises introducing, not a polynucleotide encoding mSLC, but rather a polynucleotide encoding human secondary lymphoid tissue chemokine (hSLC) (i.e., a polypeptide having the amino acid sequence of SEQ ID NO: 1) into dendritic cells acquired from an individual mammal, and then reintroducing the recombinant dendritic cells expressing the polynucleotide at the site of an established syngeneic tumor in the individual.

It follows logically that the claimed process will not be practiced using a human patient because it would be unethical, if not forbidden by law, to transplant viable tumor cells (syngeneic or otherwise) into a human in order to establish a syngeneic tumor in the individual, so as to provide a model for the study of the effects of intratumoral injections of recombinant dendritic cells.

Thus, it is apparent that the claimed process must be practiced using suitable research animals, such as, e.g., mice or guinea-pigs; but herein lays the problem. There is no factual evidence that hSLC (i.e., a polypeptide having the amino acid sequence of SEQ ID NO: 1) should be expected to function as a chemotactic factor in any species of animal other than human to attract lymphocytes or dendritic cells to the sites in the animal at which recombinant dendritic cells expressing a nucleic acid encoding hSLC are injected.

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[6] Here, it is noted that the development and use of syngeneic models, or perhaps more preferably weakly immunogenic syngeneic tumor models was widely known as of the time the application was filed. See, e.g., Shu et al. (*Cancer Res.* 1985 Apr; **45**: 1657-1662); Noguchi et al. (*Proc. Natl. Acad. Sci. USA.* 1994 Apr; **91**: 3171-3175), Nomura et al. (*Int. J. Cancer.* 2001; **91**: 597-606), and Miller et al. (*Human Gene Ther.* 2000; **11**: 53-65) (of record).

Actually there is factual evidence that the human SLC polypeptide of SEQ ID NO: 1 fails to induce chemotaxis of murine cells, which have not been engineered to express a nucleic acid encoding the hSLC receptor (i.e., human CCR7).

For example, Yoshida et al. (*J. Biol. Chem.* 1998 Mar 20; **273** (12): 7118-7122) describes experiments in which the murine pre-B cell line L1.2 was stably transfected with nucleic acid encoding human CCR7; see entire document (e.g., the abstract; and page 7119, column 1). Yoshida et al. demonstrates that although hSLC induced chemotaxis of the transfected cells expressing human CCR7, it had no detectable effect upon the migration of the parental cells, which were not transfected and did not express human CCR7; see, e.g., page 7120, Figure 4.

Because the specification fails to demonstrate that the human SLC polypeptide of SEQ ID NO: 1 binds to mouse CCR7 or any other paralog of human CCR7 found in other species of mammals suitably used to produce syngeneic tumor models, so as to act as a chemotactic, lymphocyte or dendritic cell homing factor in those mammals, and because there is factual evidence that it lacks such activity, it is submitted that the claimed process may be inoperable.

Nonetheless, even if it were later found that the human SLC polypeptide of SEQ ID NO: 1 is perhaps unexpectedly capable of binding to a receptor expressed by T lymphocytes and mature dendritic cells of another species of mammal suitably used to produce syngeneic tumor models, so as to attract those cells to the site of a tumor at which recombinant dendritic cells expressing a nucleic acid encoding the polypeptide were injected, the invention, and its use, would at best serve as a basic and/or preclinical research tool for investigative studies designed to assess those activities of hSLC and/or any therapeutic effect that might be attained from the *ex vivo* transfection of autologous dendritic cells with nucleic acid encoding the polypeptide and subsequent intratumoral injection of the transfected dendritic cells at the site of a tumor in an mammal.

Therefore, the claimed invention lacks a specific and substantial asserted utility because there is no immediate benefit upon the use of the claimed process that might

be derived by the public for a grant of a patent monopoly of the existing information disclosed in the specification.

The U.S. Supreme Court addressed the issue of utility under 35 U.S.C. § 101 in deciding *Brenner, Comr. Pats. v. Manson,* 148 U.S.P.Q. 689 (US SupCt, 1966). The Court expressed the opinion that all chemical compounds are "useful" to the chemical arts *when this term is given its broadest interpretation*; nonetheless, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The Court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. Id., at 695.

Further, the Court opined,

> [W]e are [not] blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Id., at 696.

It is submitted the instant situation is directly analogous to that which was addressed by the Court in deciding *Brenner, Comr. Pats. v. Manson*, since hereto it might be said that all investigative research tools are "useful" in the biochemical arts when the term is given its broadest interpretation, but nevertheless § 101 requires that an invention have either an immediately obvious or fully disclosed "real world" utility, which the claimed invention lacks because the specification does not disclose a currently available "real world" use for the claimed process.

To employ the disclosure of the claimed method as a tool in any endeavor other than basic and/or preclinical research would require further experimentation and development, which should be regarded as constituting part of the inventive process. Because the specification does not disclose a currently available, "real world" use for the claimed invention, the requirements set forth under 35 U.S.C. § 101 have not been met.

Notably at paragraph [0146] of the published application, the specification discloses that the claimed process has a number of uses:

> For example this method can be applied to therapeutic contexts (e.g. in the treatment of individuals suffering from a cancer). In addition, this method provides a model for dissecting the various physiological process [sic] associated with immunosurveillance, in particular the natural ability that mammals have to respond to cancers. In addition, this model can be used to study the coordinate use of various known chemotherapeutic agents, for example the effect that a specific chemotherapeutic agent has on the immune response associated with the chemotaxis of peripheral blood lymphocytes and dendritic cells to the site of a tumor in vivo.

Contrary to the asserted usefulness of the claimed process to treat cancer in individual suffering from the disease, as explained above, the claimed process utilizes a *syngeneic* tumor and will not be practiced using a human patient, for example, because it would be unethical, if not forbidden by law, to transplant viable tumor cells (syngeneic or otherwise) into a human in order to establish a syngeneic tumor in the individual, so as to provide a model for the study of the effects of intratumoral injections of recombinant dendritic cells[7].

Then, with regard to other discloses uses of the claimed process (e.g., the provision of a model for dissecting the various physiological processes associated with immunosurveillance and the natural ability that mammals have to respond to cancers), such disclosures suggest the invention is intended for use as a research tool.

However, because the claimed process may be but a mere research tool, as opposed to a process that might be used in a manner that would provide immediate benefit to the public by its practice, its application may or may not yield information that could eventually lead to the development of useful inventions.

This position substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous antitumor treatments have show exciting activity in preclinical models and yet have had minimal activity clinically; see,

[7] Moreover, since the tumor to which the claim is directed is a “syngeneic” tumor, as opposed to an “autologous” tumor, the claimed process necessarily involves the procurement of a mammal harboring a tumor established by the transfer of tumor cells from another mammal, albeit a mammal of identical genetic background; and therefore, it might be argued that the claims do not actually read on a method for treating an “autologous” tumor in a human patient, as might be done in a clinical setting.

e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skepticism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of such animal models, which may account such poor extrapolation of preclinical findings; see entire document (e.g., page 840, column 2).

Furthermore, because it remains to be determined if human SLC will function as a chemotactic factor to attract T lymphocytes and/or mature dendritic cells of some mammal suitably used for producing a syngeneic tumor model, the operability of the claimed process to achieve the claimed effect must be established before its use in any manner.

Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not "specific and substantial utilities".

To fulfill the requirements of § 101, the skilled artisan must be able to use a claimed invention in the manner asserted by Applicants' to provide some immediate benefit to the public. See *Nelson v. Bowler and Crossley*, 206 USPQ 881 (CCPA, 1980).

The existing information disclosed by Applicants' application would merely provide the artisan with an invitation to perform further investigations to discover how the claimed invention might be useful. Although such additional investigation might ultimately lead to a derivation of a specific benefit, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to enable the artisan to use the claimed process in a specific, substantial and credible manner to provide an immediate benefit to the public upon the grant of a patent. Although the disclosure of the claimed process might tomorrow command the grateful attention of the public, the Court has decided:

> [A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Brenner, Comr. Pats. v. Manson, 148 U.S.P.Q. 689 at 696 (US SupCt, 1966).

In summary, then, because the specification does not disclose a currently available, "real world" use for the claimed invention, which is specific to the nature and substance of the claimed subject matter, as disclosed, since it seems that the claimed process is at best a research tool, if indeed operable, the requirements set forth under 35 U.S.C. § 101 have not been met.

Applicant has amended claim 23 so as to be directed to a process of attracting T lymphocytes or mature host dendritic cells to a site of a *spontaneous* syngeneic tumor in a mammal, as opposed to the site of simply a syngeneic tumor.

The term "spontaneous" may be defined as meaning happening or arising without apparent external cause.

Thus, the claim, as presently amended, is drawn to a method of attracting T lymphocytes or mature host dendritic cells to a site of a syngeneic tumor in a mammal, which as arisen without apparent external cause.

Applicant has argued that the Office has failed to consider the utility of the claimed method when practiced on an individual suffering from a spontaneous syngeneic tumor, which is a tumor that arose spontaneously in a human.

In response, as explained, a human would not be said to suffer from such a tumor since tumors arising in humans are autologous tumors.

Furthermore, contrary to Applicant's remarks, the claimed process is not a process for treating cancer in a human, per se; and moreover, it is not a process comprising obtaining dendritic cells from a human, introducing a polynucleotide encoding a secondary lymphoid tissue chemokine comprising the amino acid sequence of SEQ ID NO: 1 into the dendritic cells and placing the cells at the site of the tumor in the human. Rather, as Applicant's own remarks tend to indicate, the claimed invention is an experimental process that utilizes an animal model, and not a clinical process that treats an established tumor in a human patient.

Applicant has cited the disclosure at page 17, lines 12-31, as providing support for the language of the claim, as presently amended[8]. This disclosure reads as follows:

> One of the focal issues in designing active cancer immunotherapy is that cancer cells are derived from normal host cells. Thus, the antigenic profile of cancer cells closely mimics that of normal cells. In addition, tumor antigens are not truly foreign and tumor antigens fit more with a self/altered self paradigm, compared to a non-self paradigm for antigens recognized in infectious diseases and organ transplants (see, e.g. Lewis et al., Semin Cancer Biol 6(6): 321-327 (1995)). In this context, an important aspect of the present invention is the characterization of the effects of SLC **in an animal model** where the cancer cells are spontaneous and the immune cells which respond to the cancer cells are therefore syngeneic. In this context, syngeneic is known in the art to refer to an extremely close genetic similarity or identity especially with respect to antigens or immunological reactions. Syngeneic systems include for example, **models** in which organs and cells (e.g. cancer cells and their non-cancerous counterparts) come from the same individual, and/or models in which the organs and cells come from different individual animals that are of the same inbred strain. Syngeneic models are particularly useful for studying oncogenesis and chemotherapeutic molecules. **A specific example of a syngeneic model is the CC-10 TAg transgenic mouse model of spontaneous bronchoalveolar carcinoma described herein.** In this context, artisans in the field of immunology are aware that, during mammalian development the immune system is tolerized to self antigens (e.g. those encoded by genes in the animal's germline DNA). As T-Ag is present in the germline of the transgenic animal, the transgenic animal's immune system is tolerized to this protein during maturation of the immune system.

This disclosure does not describe that subject matter, which Applicant has remarked is the subject matter to which the claims are directed (i.e., a process for treating a tumor in a human); instead it describes the use of syngeneic animal models and more particularly the CC-10 TAg transgenic mouse model of spontaneous bronchoalveolar carcinoma, which is described elsewhere in the specification[9]. It does not describe a process for attracting T lymphocytes or mature host dendritic cells to the site of a *syngeneic tumor* that arose spontaneously in a human. No, it describes the procurement and use of *an animal model* in which syngeneic tumor cells are either used to inoculate the animal or in which, due to artificially engineered expression of the SV40 large T antigen by pulmonary Clara cells, tumors bilateral multifocal pulmonary

[8] See page 13 of the amendment filed September 15, 2009.
[9] Notably, the specification describes the CC-10 TAg transgenic mouse model as producing spontaneous bronchoalveolar carcinomas, such that its use "avoids the problems associated with the use of cell lines that have been subjected to specific (and non-specific) selective pressures during their period in cell culture" (page 19, lines 24-28).

adenocarcinomas develop in particular mice, which later die at 4 months as a result of progressive pulmonary tumor burden[10].

Again, as before noted, the term “syngeneic" is a term of art, which, when used in the context of the language of the claim, describes a tumor or a tumor cell line that originated in and was derived from an animal of an identical genetic background as the animal into which the same tumor cells are inoculated (transplanted) so as to establish a tumor in the animal for the purposed of modeling the pathology of the disease associated with the tumor. However, as is apparently the case with the CC-10 TAg transgenic mouse model of spontaneous bronchoalveolar carcinoma, the lung tumor cell originates in the host animal itself (i.e., within the same individual animal). Even so, the disclosure of this transgenic mouse model in which an oncogene is ectopically expressed under the control of a pulmonary cell type-specific promoter, so as to cause epithelial lung tumors to arise spontaneously in the mice after 16-20 weeks (post-natal)[11], does not suffice to describe a method of treating a human patient that is suffering from a lung tumor or for that matter, any other type of tumor. In the “real-world” in which the specific and substantial asserted utility of the claimed invention must be accessed, a human patient is never described as an “animal model”.

At page 14 of the amendment filed September 15, 2009, Applicant has remarked that the disclosure at page 20, line 24-28, describes an advantage of animal models, such as the CC-10 TAg transgenic mouse model of spontaneous bronchoalveolar carcinoma.

More particularly, the disclosure reads as follows:

> As **the transgenic mouse model** [emphasis added] that is <u>used herein</u> [underscoring added] does not expose the animal's immune system to non-self antigens, does not mix cells and tissue from strains of mice that have been observed to have different immunological characteristics and is instead directed to evaluating an immune response to spontaneous tumors, the data provided by this model is clinically relevant in the context of human cancers.

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[10] See, e.g., Sharma et al. (*Hum. Gene Ther.* 2003 Nov 1; **14** (16):1511-1524), which describes the CC-10 TAg transgenic mouse model.

[11] See Magdeleno et al. (*Cell Growth Differ.* 1997 Feb; **8** (2): 145-155) (of record; cited by Applicant).

At best, this disclosure suggests that the CC-10 TAg transgenic mouse model of spontaneous bronchoalveolar carcinoma, or similar models, are appropriately used to evalulate clinical methods of treating cancer in humans – but it does not teach or suggest that the human patient should be treated as an "animal model" or that a human should be genetically engineered so as to cause in the human the spontaneous development of syngeneic (or more properly *autologous*) tumors.

Then, also at page 14 of the amendment filed September 15, 2009, Applicant has argued that the additional disclosures at page 12, lines 16-25, and page 57, lines 2-21, support their assertion that the claimed invention satisfies the utility requirement set forth under 35 U.S.C. § 101 because attracting T lymphocytes or mature host dendritic cells to a site of a spontaneous syngeneic tumor in a human, in order to attract lymphocytes to the site of the tumor, is an event that will reduce tumor burden in the human.

In initial response, as explained above, because it remains to be determined if human SLC will function as a chemotactic factor to attract T lymphocytes and/or mature dendritic cells of some mammal (not a human) suitably used for producing a syngeneic tumor model, the operability of the claimed process to achieve the claimed effect must be established before its use in any manner. Otherwise the claimed invention cannot be used in a manner that satisfies the instant requirements for patentability. Nonetheless, it is submitted that the claimed process, when properly construed in light of the disclosure, is actually a research tool, not a clinical process that can be used to treat cancer in human patients. As explained, although additional investigation using the claimed invention as a research tool might ultimately lead to a derivation of a specific benefit, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to enable the artisan to use the claimed process in a specific, substantial and credible manner to provide an immediate benefit to the public upon the grant of a patent.

It is apparently Applicant's contention that the disclosure at page 12, lines 16-25, supports their assertion that the claimed invention can be used to treat tumors in human

patients by causing a reduction in tumor burden as a result of having attracted T lymphocytes and mature dendritic cells to the sites of tumors in the patients.

The disclosure at page 12 reads as follows:

> Using transplantable murine lung cancer models, we show that the antitumor efficacy of SLC is T cell-dependent. In these transplant models, the antitumor efficacy of SLC was determined using transplantable tumors propagated at s.c. sites. In the transplantable models, recombinant SLC administered intratumorally led to complete tumor eradication in 40% of the treated mice. The SLC-mediated antitumor response was dependent on both CD4 and CD8 lymphocyte subsets and was accompanied by DC infiltration of the tumor. In recent studies that directly support the antiangiogenic capacity of this chemokine, Arenberg et al. (Arenberg et al., Cancer Immunol. Immunother., 49:587-592, 2000) have reported that SLC inhibits human lung cancer growth and angiogenesis in a SCID mouse model.

As promising as such preclinical results may be it is submitted that such a disclosure fails to provide sufficient factual evidence of the asserted utility of the claimed process to obviate this rejection since the invention is not a method of treating spontaneously arising lung tumors in mice or humans, per se; rather it appears that the claimed invention is a research tool, which is described in this application as a process that may be used to further consider whether or not a similar process might be used to treat lung cancer in humans and other mammals.

Then, too, as already explained, there is no factual evidence disclosed in this application that supports an assertion that hSLC (i.e., a polypeptide having the amino acid sequence of SEQ ID NO: 1) should be expected to function as a chemotactic factor in any species of animal other than human to attract lymphocytes or dendritic cells to the sites in the animal at which recombinant dendritic cells expressing a nucleic acid encoding hSLC are injected.

Actually there is factual evidence that the human SLC polypeptide of SEQ ID NO: 1 fails to induce chemotaxis of murine cells, which have not been engineered to express a nucleic acid encoding the hSLC receptor (i.e., human CCR7).

For example, as explained, Yoshida et al. (*supra*) describes experiments in which the murine pre-B cell line L1.2 was stably transfected with nucleic acid encoding human CCR7; see entire document (e.g., the abstract; and page 7119, column 1). Yoshida et al. demonstrates that although hSLC induced chemotaxis of the transfected cells

expressing human CCR7, it had no detectable effect upon the migration of the parental cells, which were not transfected and did not express human CCR7; see, e.g., page 7120, Figure 4.

Because the specification fails to demonstrate that the human SLC polypeptide of SEQ ID NO: 1 binds to mouse CCR7 or any other paralog of human CCR7 found in other species of mammals suitably used to produce syngeneic tumor models, so as to act as a chemotactic, lymphocyte or dendritic cell homing factor in those mammals, and because there is factual evidence that it lacks such activity, it is submitted that the claimed process may be inoperable.

Nonetheless, even if it were later found that the human SLC polypeptide of SEQ ID NO: 1 is perhaps unexpectedly capable of binding to a receptor expressed by T lymphocytes and mature dendritic cells of another species of mammal suitably used to produce syngeneic tumor models, so as to attract those cells to the site of a tumor at which recombinant dendritic cells expressing a nucleic acid encoding the polypeptide were injected, the invention, and its use, would at best serve as a basic and/or preclinical research tool for investigative studies designed to assess those activities of hSLC and/or any therapeutic effect that might be attained from the *ex vivo* transfection of autologous dendritic cells with nucleic acid encoding the polypeptide and subsequent intratumoral injection of the transfected dendritic cells at the site of a tumor in an mammal.

Therefore, the claimed invention lacks a specific and substantial asserted utility because there is no immediate benefit upon the use of the claimed process that might be derived by the public for a grant of a patent monopoly of the existing information disclosed in the specification.

Applicant has also referred to the disclosure at page 57, lines 2-21, as providing support for the assertion that the claimed invention can be used to reduce tumor burden in humans.

This disclosure reads as follows:

> Yet another embodiment of the invention is a method of inhibiting the growth of spontaneous mammalian cancer cells in a population of syngeneic CD8 positive T cells,

> CD4 positive T cells and Antigen Presenting Cells by exposing the population of cells to an amount of secondary lymphoid tissue chemokine (SLC) polypeptide sufficient to inhibit the growth of the cancer cells. A closely related embodiment of the invention is a method of treating a syngeneic cancer in a mammalian subject comprising administering a therapeutically effective amount of an SLC to the subject. In preferred methods the SLC is human SLC. In highly preferred methods the SLC has the polypeptide sequence shown in SEQ ID NO: 1. Preferably, the SLC polypeptide is administered to a mammal via intratumoral injection, or via intra-lymph node injection. In yet another mode of administration, an expression vector having a polynucleotide encoding a SLC polypeptide is administered to the mammal and the SLC polypeptide is produced by a syngeneic mammalian cell that has been transduced with an expression vector encoding the SLC polypeptide. In a highly preferred embodiment, the cells are exposed to a SLC polypeptide that is expressed by a mammalian cell that has been transduced with an expression vector encoding the SLC polypeptide. A related embodiment of the invention consists of syngeneic host cells that have been transduced with an expression vector encoding the SLC polypeptide. In highly preferred embodiments of this aspect of the invention, the syngeneic host cells have been transduced with an expression vector encoding the SLC polypeptide in vivo.

This disclosure appears to describe a method of treating an syngeneic tumor in a mammalian subject, including a human; but as explained, the claims are not properly construed as reading on such a process for treating autologous (as opposed to syngeneic) tumors in humans. Instead the claims are properly construed in light of relevant disclosures in the specification as reading on an experimental process utilizing *an animal model* (not a human patient), such as the CC-10 TAg transgenic mouse model of spontaneous bronchoalveolar carcinoma. As explained, the claimed invention is thus a tool for research intended for use in determining if a similar process might be used to treat cancer in humans; and as a mere research tool, the claimed process fails to satisfy the utility requirement set forth under 35 U.S.C. § 101.

In further response, it is submitted that no tumors actually arise "spontaneously" in humans because human are not genetically engineered to unconditionally develop tumors as does the described the CC-10 TAg transgenic mouse model of spontaneous bronchoalveolar carcinoma; moreover, in general, in the real-world and outside the experimental world of the research laboratory, a tumor arises by influence of any number of genetic or environmental factors (e.g., mutations in the alleles of a gene encoding a tumor suppressor or proto-oncogene). Although it is perhaps argued that many such tumors arise without apparent external cause, there is a wealth of data to indicate that external (environmental) factors play a significant role in oncogenesis.

Consider, for example, the lung cancer that develops largely as a consequence of genetic alterations caused by exposure to asbestos, cigarette smoke, and other such mutagens.

In final response to Applicant's arguments traversing the propriety of this ground of rejection, although the Example 4 describes the use of the CC-10 TAg transgenic mouse model of spontaneous bronchoalveolar carcinoma to evaluate the antitumor effects of using the claimed process to attract immune cells to the site of tumors in the mice, it does not change the fact the claim is not directed to a process of treating an autologous tumor in a human patient.

Perhaps Applicant should consider filing a continuation of this application in which the claims are directed to the subject matter that Applicant has remarked is the invention, namely a process of treating an established tumor in a human patient[12].

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The further rejection of claim 32 under 35 U.S.C. 112, first paragraph, is maintained. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Beginning at page 15 of the amendment filed September 15, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive of the following reasons:

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[12] Notably, such a tumor will not be described as the artisan as "syngeneic". It might be described as "autologous" and it might be described as "sporadic" (as opposed to spontaneous), though not all tumors are sporadic since some tumors familial and arise in the patient that is predisposed to the development of the tumor.

As explained in the above rejection, since the claimed invention could not be used in a manner that would provide any immediate benefit to the public without need of first elaborating a real-world use for the process, which could provide that benefit to the public, it fails to satisfy the utility requirement.

Any need to elaborate a utility for the claimed process before the invention could be used to achieve immediate benefit from its practice would constitute a need to perform undue and unreasonable experimentation. As such, the claims also fail to satisfy the enablement requirement set forth under 35 U.S.C. § 112, first paragraph.

As before explained, M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Accordingly, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), and given the claimed

invention's evident lack of utility under § 101, it is submitted that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to have enabled the skilled artisan to have used the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

New Ground of Rejection

Claim Rejections – 35 U.S.C. § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claim 32 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the reply filed September 15, 2009. In that paper, applicant has stated the invention has utility because it can be used to treat tumors in human patients, and this statement indicates that the invention is different from what is defined in the claim(s) because, as explained, the claim is directed to an experimental process that utilizes a syngeneic animal model, not a therapeutic process that involves treating an autologous tumor in a human patient.

Conclusion

10. No claim is allowed.

11. As before noted, the prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Kirk et al. (of record) teaches augmentation of dendritic cell-based immunotherapy by murine SLC using an allogeneic tumor model. Chan et al. (*Blood*. 1999; **93**: 3610-3616) (of record; cited by Applicant) teaches human SLC is chemotactic for mature dendritic cells. Willimann et al. (*Eur. J. Immunol.* 1998; **28**: 2025-2034) (of record; cited by Applicant) teaches human SLC acts as a

chemoattractant via CCR7 to attract activated T cells. Nomura et al. (*Anticancer Res.* 2000; **20**: 4073-4080) reviews SLC. Nishioka et al. (*Cancer Res.* 1999 Aug 15; **59**: 4035-4041) teaches intratumoral injection of recombinant dendritic cells expressing IL-12 induces antitumor immunity. Hirao et al. (*Cancer Res.* 2000 Apr 15; **60**: 2209-2217) teaches inoculation of recombinant dendritic cells expressing CCR7 at the site of a tumor in a syngeneic tumor model. Tirapu et al. (*Cur. Gene Ther.* 2002; **2**: 79-89) teaches cytokine, including IL-12 and SLC, encoding nucleic acid transfer into dendritic cells for intratumoral delivery.

Newly cited, Baratelli et al. (*J. Transl. Med.* 2008 Jul 22; **6**: 38) describes pre-clinical characterization of GMP grade CCL21-gene modified dendritic cells for application in a phase I trial in Non-Small Cell Lung Cancer.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

slr
December 6, 2009